Cellular Host Receptors of Arboviruses Causing Hemorrhagic Fever: Scientific Review

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Abstract:

Arboviruses that cause hemorrhagic fever are a wide range of RNA viruses that are mostly spread by insects and other arthropods. How well they interact with certain cellular receptors determines how well they can infect human host cells. Recent research has identified several novel cellular host receptors utilized by different arboviruses to penetrate target cells, a process essential for viral replication and subsequent pathogenesis. The human transferrin receptor 1 (TfR1) is very important for New World clade B arenaviruses, which cause hemorrhagic fevers, to get in. Pathogenic arenaviruses, including Machupo and Junin viruses, exploit human TfR1, whereas closely related nonpathogenic viruses utilize TfR1 orthologs from their natural reservoir hosts. Changes in TfR1 can make it easier or harder for someone to get sick. This means that zoonotic diseases could happen if the host receptor changes.

Viral glycoproteins Gn and Gc help the virus attach to host cells. Clathrin helps CCHFV get into cells. Cholesterol and pH levels can affect this process. Nucleolin on the surface of host cells and DC-SIGN lectin on dendritic cells may also be involved. These interactions facilitate the infection of macrophages, dendritic cells, and epithelial cells, which are crucial for viral dissemination and immune evasion. Several types of receptors have been linked to other arboviruses, such as dengue virus (DENV), West Nile virus (WNV), and others that cause symptoms of hemorrhagic disease. These include Fc gamma receptors (FcγRs), which help antibody-dependent enhancement, different types of lectins like C-type lectins (DC-SIGN), integrins (αvβ3 integrin), laminin receptors, and glycosaminoglycans like heparan sulfate. These

receptors often enable viral adherence and invasion of immune or endothelial cells, thereby affecting viral tropism and hemorrhagic pathogenesis.

The redundancy and diversity of receptor molecules employed by arboviruses highlight the complexity of virus-host cell interactions and suggest evolutionary adaptations that facilitate spillover and the emergence of diseases. Understanding these new cellular receptors is important for coming up with antiviral strategies that can stop viruses from getting into cells. However, targeting these receptors is risky because of their normal functions.

New cellular host receptors for arboviruses that cause hemorrhagic fever include human transferrin receptor 1 for New World arenaviruses, clathrin-mediated entry receptors possibly involving nucleolin and DC-SIGN for Crimean-Congo Hemorrhagic Fever Virus, and various Fc receptors, lectins, integrins, laminin receptors, and glycosaminoglycans for flaviviruses and other arboviruses. These findings improve the molecular understanding of hemorrhagic fever virus entry and pathogenesis, presenting both opportunities and challenges for therapeutic intervention.

Keywords: Arboviruses, hemorrhagic fever, Host Receptors, Arthropod-borne viruses, Arboviruses ligand-receptors.

Introduction:

Arthropod-borne viruses (arboviruses) encompass numerous critical human pathogens that cause hemorrhagic fevers, a category of severe diseases marked by fever, bleeding diathesis, and involvement of multiple organs. Comprehending the cellular host receptors that arboviruses utilize to penetrate target cells is essential for clarifying viral pathogenesis and formulating antiviral therapeutics and vaccines. This review seeks to encapsulate recent findings concerning novel cellular receptors for arboviruses that induce hemorrhagic fever, elucidating their functions in viral adhesion, internalization, and the modulation of host immune responses. Arthropod-borne pathogens account for over 17% of infectious diseases, impacting millions globally annually and significantly influencing the emergence of novel human pathogens.

Dengue, the most prevalent arboviral disease, results in approximately 90 million cases and about 40,000 deaths a year [**1**]. Emerging arboviruses such as *Phlebovirus riftense* (Rift Valley

fever virus), *Alphavirus mayaro* (Mayaro fever virus), *Orthoflavivirus nilense* (West Nile fever virus), *Alphavirus chikungunya* (Chikungunya fever virus), and *Orthoflavivirus encephalitidis* (tick-borne encephalitis virus) have also garnered scientific attention as public health concerns [2]. Arboviruses are a diverse group of more than 500 viruses transmitted by arthropod vectors such as mosquitoes and ticks [3] present on several continents. In the Southeast Asian region, the presence of *Orthoflavivirus denguei*, or dengue fever virus (DENV), and *Orthoflavivirus japonicum*, or Japanese encephalitis virus (JEV), probably due to anthropogenic actions and geographic changes, is the result of a "spillover" of natural zoonotic pathogens into the human population [2,4].

Cellular host receptors of arboviruses, specifically those causing hemorrhagic fever:

New World clade B arenaviruses known to cause hemorrhagic fever in humans utilize human TfR1 for cell entry. TfR1 is a cellular receptor involved in iron uptake and is highly significant in viral replication and pathogenesis of hemorrhagic fever viruses such as Machupo virus (MACV), Junin virus (JUNV), Guanarito virus (GTOV), and Sabia virus (SABV). Nonpathogenic arenaviruses related to hemorrhagic fever viruses use orthologs of TfR1 from their respective natural hosts. This receptor is rapidly endocytosed, expressed on endothelial cells, and upregulated on activated lymphocytes, facilitating viral hemorrhagic fever development **[5]**.

Integrins, heterodimeric glycoproteins (e.g., αvβ3 integrin), have been implicated as functional receptors for certain arboviruses including West Nile virus. Laminin receptors (37-67 kDa), including nonintegrin laminin receptors, have been identified as receptors for dengue virus serotypes and tick-borne encephalitis virus (TBEV). These receptors aid viral attachment and entry in host cells **[6]**. DC-SIGN (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin), a C-type lectin receptor on dendritic cells, is proposed as an entry factor for Crimean-Congo hemorrhagic fever virus (CCHFV). This receptor mediates early virus attachment and promotes viral entry through interaction with viral glycoproteins Gn and Gc **[7]**.

Nucleolin, primarily a nucleolar protein, has been suggested as a putative entry factor for CCHFV, although more investigation is necessary to confirm its role in viral internalization **[6]**. Glycosaminoglycans and Heparan Sulfate, a highly conserved sulfated polysaccharides on cell

surfaces serve as attachment factors for numerous arboviruses, including dengue virus, Sindbis virus, Japanese encephalitis virus, and Ross River virus, facilitating viral adsorption and entry **[6]**.

There are other Molecules such as α-dystroglycan: Used by several Old-World arenaviruses and some New World arenaviruses as a receptor. Glucose-Regulated Protein 78 (GRP78): Identified as a receptor for dengue virus serotype 2 in hepatic cells **[6]**. spectrum of host receptors critical for cellular entry of hemorrhagic fever arboviruses, including newer understandings of receptor usage diversity among arenaviruses and other flaviviruses or bunyaviruses causing hemorrhagic disease.

Different host receptors have been linked to arbovirus attachment and entry. Some examples are lectins, integrins, laminin receptors, and Fc gamma receptors (FcγRs). Flaviviruses, including dengue virus (DENV), West Nile virus (WNV), and yellow fever virus (YFV), employ distinct cellular receptors to facilitate their entry into host cells. The αvβ3 integrin, a crucial receptor on endothelial cells, has been recognized as a functional receptor for West Nile Virus (WNV), enabling viral attachment and internalization via receptor-mediated endocytosis. Lectins, such as DC-SIGN and mannose receptors on dendritic cells, facilitate flavivirus attachment and entry through interactions with viral envelope glycoproteins **[8]**.

Antibody-dependent enhancement (ADE) of infection via FcγRs I, II, and III on immune cells is crucial in dengue pathogenesis. These receptors can bind to DENV-antibody complexes, which makes it easier for the virus to get into and reproduce in monocytes and macrophages. This can cause serious illness. Besides FcγRs, scientists have found other non-Fcγ receptors that can cause ADE. This means that there is more than one way to make an infection worse. Alphaviruses, like the chikungunya virus and the Ross River virus, use cellular receptors like laminin and integrins to get into cells. Laminin receptors have been shown to bind Ross River virus, which supports the virus's preference for muscle and joint tissues that are associated with disease symptoms **[8]**.

Arboviruses, like the dengue virus, also attack host cellular cytoskeletal proteins like dynein and myosin to help move things around inside cells and build replication complexes. Arboviral infection can modify lipid metabolism, immune signaling, and the production of reactive oxygen species (ROS) in host cells, thereby promoting viral replication and undermining the host's defenses against the virus. Wolbachia endosymbionts in mosquito vectors have diverse impacts on

the host cytoskeleton. They block proteins that are important for arboviruses to attach to and enter cells. This stops the virus from spreading and making other people sick **[8]**. The process by which arboviruses get into host cells is complicated and involves different kinds of receptors that are different for each virus family and cell type. Scientists can now treat arboviral infections in new ways and learn more about how these viruses make people sick by finding these receptors.

Human ligands and proteins implicated in hemorrhagic yellow fever encompass viral envelope proteins facilitating cellular adhesion, interferon signaling components (STAT1, STAT2), innate immune sensors (TLRs, RIG-I, MDA5), cytokines and apoptosis proteins associated with immune dysregulation, and T cell populations essential for infection control yet also contributing to pathogenesis. The envelope protein is very important for how viruses spread and how they interact with host receptors that affect. Flaviviruses such as Dengue virus (DENV), Zika virus (ZIKV), West Nile Virus (WNV), and Yellow Fever virus (YFV) bind cellular receptors including C-type lectins (DC-SIGN, L-SIGN), mannose receptor, and glycosaminoglycans like heparan sulfate for attachment and entry **[10]**.

Alphaviruses, including the Chikungunya virus (CHIKV), utilize Mxra8 as an entry receptor that facilitates viral attachment and internalization **[8]**. The Crimean-Congo hemorrhagic fever virus (CCHFV), a bunyavirus, interacts with cellular receptors like DC-SIGN and nucleolin. But its use of receptors is not as clear as that of flaviviruses and alphaviruses **[10]**. Integrins, laminin receptors, and phosphatidylserine receptors from the TIM and TAM families are also thought to be arboviral receptors. They help viruses get into cells by attaching to enveloped viruses that look like apoptotic bodies **[12]**. Arboviruses use mosquito vector cellular proteins like actin, tubulin, and dystroglycan to get into and move around inside the arthropod host **[13]**. MXRA8 for arthritogenic alphaviruses such as CHIKV and LDLRAD3 for VEEV were identified via CRISPR/Cas9 loss-of-function screens. This makes it easier for viruses to get into cells. These receptors help the process of binding and getting inside. Most of the time, this happens through endocytosis that is mediated by clathrin. In this process, the low pH in endosomes changes the shape of E1-E2 glycoproteins, which makes the membranes stick together and RNA come out. Attachment factors such as heparan sulfate, C-type lectins, and phosphatidylserine receptors (like TIM-1) bring virions to cell surfaces before receptors interact. **[14]**.

Important receptors for major arboviruses: Through E1-E2 clefts, MXRA8 connects to CHIKV, MAYV, RRV, ONNV, and SFV. Cryo-EM structures show that Ig-like domains fit into spikes, which makes it easier for the virus to get inside. Knockout mice have fewer infections in their bones and muscles. VEEV needs LDLRAD3 to get into neurons. CRISPR screens in N2a cells identified it as the most effective candidate, demonstrating direct binding and uptake. VLDLR and ApoER2 help EEEV, SFV, and SINV get into cells. Low-density lipoprotein receptors make it easier for avian and mammalian cells to get infected. Others: Laminin receptor and NRAMP2 for SINV; PHB1 and CD147 suggested for CHIKV through biochemical assays, necessitating additional validation **[15]**. Molecular mechanisms of entry and replication: Once they attach, arboviruses bind to receptors, which makes endocytosis happen. When the endosome becomes acidic, it breaks up E2-E1 heterodimers, which opens up E1 fusion loops for hemifusion and pore formation. Released genomic RNA translates nonstructural proteins (nsP1-4) to create a replication complex that makes negative-strand intermediates for genomic and subgenomic RNAs that code for structural proteins. Plasma membranes make new virions, which then get E2-E1 spikes. **[16]**.

Cell surface molecules used by arboviruses

Primary attachment/lectin receptors (glycan recognition). Many flaviviruses and some alphaviruses present N-linked glycans on envelope proteins that bind C-type lectins on dendritic cells (DC-SIGN/CD209) or related receptors, concentrating virions for productive uptake. **[17]**. **Heparan sulfate proteoglycans (HSPGs).** Electrostatic interactions between basic patches on viral envelope proteins and cell-surface glycosaminoglycans can serve as low-affinity, high-avidity attachment factors that influence tropism and adaptation in cell culture. **[18]**. **Phosphatidylserine (PtdSer) receptors (TIM/TAM families).** Enveloped virions can display PtdSer in their membrane; TIM family proteins bind PtdSer directly, while TAM family receptor tyrosine kinases (AXL, TYRO3, MER) bind indirectly through bridging ligands (Gas6/Protein S) and thereby promote viral uptake and immune modulation. **[19]**.

Specific proteinaceous receptors (high-affinity entry receptors). Examples include MXRA8 for arthritogenic alphaviruses (e.g., chikungunya virus), which acts as a bona fide entry receptor with a defined structural interface to the viral E1–E2 spike. **[20]**.

MXRA8 — a structurally characterized alphavirus entry receptor: High-resolution X-ray and cryo-EM studies show the MXRA8 ectodomain comprises **two Ig-like domains** in a strand-swapped, disulfide-stabilized head-to-head arrangement; the molecule is bowed and presents a hinge/stalk critical for engagement. This unusual topology orients MXRA8 to wedge into a cleft on the virion surface. **[20]**. **Binding mode to CHIKV E spike.** MXRA8 binds in the canyon formed between two adjacent E2–E1 heterodimers of a single trimeric spike and also contacts a neighboring spike; two binding modes were observed in immature-like virus-like particles but only the high-affinity mode is seen with mature infectious CHIKV. Key contact residues on both MXRA8 and the viral E protein explain species-specific differences and the effect of viral maturation on receptor accessibility. The structural placement of MXRA8 explains how a single receptor can bridge spikes and influence the geometric constraints of receptor engagement, thereby determining cell tropism and providing a clear target for small-molecule or antibody inhibitors that block the MXRA8–E interface. Structural coordinates and PDB depositions (e.g., PDB 6JO8 and related entries) document the atomic contacts used for inhibitor design. **[20]**.

Phosphatidylserine receptors (TIM/TAM) and "apoptotic mimicry"

Mechanism (general). Many enveloped arboviruses expose PtdSer on their lipid envelope; TIM receptors (TIM-1/-3/-4) directly recognize PtdSer through a conserved pocket (MILIBS motif) and promote virus internalization, while TAM receptors require bridging ligands (Gas6/ProS) that bind viral PtdSer and activate the TAM RTK for uptake and suppression of local antiviral responses. This "apoptotic mimicry" both facilitates entry and can dampen innate signaling. **[19]**. **TIM-1 specific data.** Genetic ablation and mechanistic studies show TIM-1 contributes directly to dengue virus endocytosis and productive infection; TIM-1 ubiquitination was shown to be required for efficient internalization in some cell models, underlining that receptor post-translational regulation influences entry efficiency. **[21]**.

Lectin receptors (DC-SIGN) and glycan-mediated attachment

DC-SIGN as a model. DC-SIGN (CD209), a C-type lectin on dendritic cells, recognizes high-mannose N-linked glycans on flavivirus E proteins and concentrates virions on the cell surface; this enhances the probability of interacting with secondary entry factors and is important for

infection of immature dendritic cells. Structural reconstructions of virions complexed with DC-SIGN fragments illustrate glycan-mediated docking. **[22]**.

Heparan sulfate proteoglycans (HSPGs) and electrostatic attachment

Role and adaptation. HSPGs act as low-specificity attachment factors via electrostatic contacts; clinical and lab strains differ in HSPG usage, and increased HSPG binding is often associated with cell-culture adaptation and altered virulence/tropism. Blocking HSPG interactions can reduce infectivity in endothelial and other target cells. **[18]**.

From attachment to membrane fusion — cellular uptake routes

A unifying model for many arboviruses: (i) low-affinity attachments (HSPG, lectins) concentrate virions; (ii) high-affinity receptors or PtdSer receptors promote clustering and trigger **clathrin-mediated endocytosis** (or alternative endocytic routes depending on virus and cell type); (iii) acidification and conformational changes in viral fusion proteins (class II fusion proteins for flaviviruses and alphaviruses) mediate membrane merger in late endosomes. The precise receptor repertoire and post-binding signaling (e.g., AXL kinase activity) can influence whether infection proceeds or is aborted. **[23]**.

Molecular structures of arbovirus receptors (notably the MXRA8–alphavirus complex) and mechanistic dissection of attachment and uptake (lectin recognition, HSPG binding, PtdSer-receptor mediated uptake, and RTK involvement) have markedly advanced our understanding of entry. These structural and mechanistic insights guide rational antiviral strategies — from receptor decoys and blocking antibodies to inhibitors targeting receptor–virus interfaces — but translating them safely requires careful attention to receptor physiological roles and in vivo context.

Receptor-mediated entry

Attachment factors (heparan sulfate, C-type lectins) concentrate virions at the cell surface but often do not by themselves trigger productive entry. Secondary/entry receptors engage viral surface proteins and induce the conformational changes or signaling required for internalization. The canonical sequence is: attachment → receptor engagement → internalization (commonly clathrin-mediated endocytosis for flaviviruses) → endosomal maturation and low-pH-triggered membrane fusion (for many enveloped arboviruses) → uncoating and genome release. **[24,25]**.

Alphaviruses — a structural receptor paradigm (MXRA8)

Discovery and importance: A genome-wide CRISPR screen identified **MXRA8** (matrix-remodeling associated protein 8), a cell-adhesion-like Ig-superfamily protein, as an entry mediator for arthritogenic alphaviruses (e.g., chikungunya, Mayaro, Ross River, O'nyong-nyong), and blocking MXRA8 reduces infection in cells and animals. **[26]**. Molecular architecture: MXRA8 contains two Ig-like domains connected by a hinge and a membrane proximal stalk. High-resolution crystal and cryo-EM structures of MXRA8 bound to chikungunya virus (CHIKV) envelope glycoprotein E1–E2 show MXRA8 docks into a "canyon" formed between two adjacent E protein protomers on the viral surface, contacting residues on E1 and E2 across two protomers. The receptor-binding footprint spans both Ig domains and the hinge, explaining how a single receptor molecule bridges receptor surface glycans and protein epitopes. **[27,28]**.

Functional consequences: MXRA8 engagement stabilizes a receptor-bound state that promotes virus internalization; mutations in viral E2 or in MXRA8's binding surfaces decrease infectivity or change host specificity. Structural data explain species-specific differences in susceptibility and guide therapeutic strategies (Mxra8-Fc decoy proteins or blocking antibodies). **[24,27,28]**.

Flaviviruses — heterogeneous receptors and phosphatidylserine (PS)-mediated uptake

Classical lectin receptors and proteoglycans: Dengue virus (DENV) and related flaviviruses use **DC-SIGN (CD209)** on dendritic cells and heparan sulfate proteoglycans as high-affinity attachment factors; DC-SIGN binding to high-mannose glycans on the E protein enhances capture and may facilitate entry in target cells. **[29]**. TIM/TAM family and "apoptotic mimicry": Flaviviruses often display or acquire phosphatidylserine (PS) in their viral envelope and exploit host PS receptors (TIM family and TAM receptor tyrosine kinases via Gas6/Protein S bridging) to enhance uptake — a process called apoptotic mimicry. TIM/TAM engagement typically acts as an entry-enhancing pathway rather than an obligate receptor in all cell types, and it can modulate innate immune signaling. **[30]**. AXL and Zika virus — a contested receptor: AXL (a TAM family kinase) was reported to promote Zika virus (ZIKV) infection in some human cell types, but subsequent work showed mixed results — in many primary cell systems AXL behaves as an attachment/immune-modulatory factor rather than an essential entry receptor. The role of AXL

varies by cell type, developmental stage and species; some recent data continue to refine this model. **[31]**.

Structural and mechanistic themes across arboviruses

Multivalent, low-affinity to high-avidity: Virions exploit multivalency — arrays of envelope proteins and multivalent glycans — to convert individually weak interactions into high-avidity binding to cell surfaces, permitting reversible "scanning" before productive receptor engagement. **[32,33]**. Receptors often bind quaternary epitopes: Structural reconstructions show many receptors recognize quaternary surfaces that exist only on assembled virions (for example, MXRA8 bridges two adjacent E protomers); this explains why isolated viral subunits or monomeric proteins can fail to recapitulate receptor binding. **[27,28]**. Triggering internalization and fusion: Receptor engagement can directly trigger endocytosis or simply concentrate particles until they are internalized by constitutive pathways (clathrin-mediated endocytosis, macropinocytosis, caveolar pathways depending on virus/cell). For many enveloped arboviruses, low endosomal pH or other endosomal cues then trigger E1/E2 (alphaviruses) or E glycoprotein (flaviviruses) rearrangements leading to membrane fusion. Cryo-EM studies document the acid-triggered conformational changes that expose fusion loops and drive membrane merger. **[24]**.

Implications for tropism, pathogenesis and therapeutics

Receptor expression patterns in tissues (e.g., synovial fibroblasts and MXRA8 for alphaviruses; dendritic cells, neural progenitors and varying PS-receptor expression for flaviviruses) largely determine which cell types a virus infects and the disease manifestations observed. Structural receptor maps explain cross-species tropism and host barriers. **[26,27,33]**. Therapeutic targeting: High-resolution virus–receptor complexes have motivated development of receptor-decoys (e.g., MXRA8-Fc), blocking monoclonal antibodies, and small molecules that interfere with receptor engagement or downstream endocytic pathways. However, the redundancy of attachment factors and cell-type variability means that blocking a single receptor may not fully abrogate infection in all tissues. **[26,27,33]**. Genome-wide CRISPR screens and haploid genetic screens objectively identify host factors necessary for infection (for instance, the discovery of MXRA8). High-throughput proteomics, virus-overlay binding assays, and single-particle cryo-EM facilitate the mapping of contact residues and glycan dependencies. Comparative structural biology

of related arboviruses shows that they have similar receptor footprints and unique insertions that change how receptors are used. Ongoing work continues to nominate new receptors for bunyaviruses, orthobunyaviruses and insect-specific arboviruses. **[25,33,24]**.

Molecular-level understanding of arbovirus–receptor interactions has matured from candidate receptor lists to atomic structures that explain tropism, species specificity, and steps of entry. Alphavirus MXRA8 provides a clear structural example of a receptor that binds a quaternary site on the virion; flaviviruses instead use a repertoire of lectins, PS-binding receptors and attachment factors with more cell-type dependence. Continued integration of genetic screens with cryo-EM and cell biology will reveal additional "novel" receptors and clarify which interactions are essential versus accessory — information that is crucial for rational antiviral design. **[26,32]**. pr/E3 occupancy in alphaviruses) modulates receptor site exposure; dynamic structural snapshots of intermediate maturation states will clarify when and how receptors access specific epitopes. The MXRA8 studies already show maturation influences high- vs low-affinity modes. **[33]**. Pecies-specific receptor sequence differences alter susceptibility; mapping polymorphisms and their structural consequences informs zoonotic potential and animal model selection. **[34]**. Arboviruses (arthropod-borne viruses) engage host cells through specific interactions between viral attachment proteins and one or more cellular receptors or attachment factors; these molecular interactions determine binding specificity (which receptor(s) are recognized), affinity (strength of interaction), and ultimately tropism (which cell types, tissues, and species the virus infects). **[35]**.

Molecular specificity: determinants of receptor recognition

Protein–protein interfaces and receptor architecture: Alphaviruses (e.g., chikungunya, Mayaro) bind the host receptor MXRA8 via a well-defined interface on the viral E1/E2 glycoprotein complex; the receptor's two Ig-like extracellular domains present a complementary surface that dictates high positional specificity. **[36]**. Glycan-mediated contacts and attachment factors: For many flaviviruses (e.g., dengue, Zika), initial attachment is often mediated by glycans (heparan sulfate) or C-type lectins (DC-SIGN), which broaden apparent tropism by increasing the pool of permissive cells, but true entry sometimes requires secondary protein receptors. **[37]**. Multiple and redundant receptors: Some arboviruses use more than one host factor (e.g., AXL, TIM, TYRO3 family members implicated in Zika/dengue interactions), producing cell-type dependent receptor usage and complicating a one-receptor = one-tropism model. **[38]**.

Binding strength shapes entry and tropism

Quantitative binding matters: Measured affinities (e.g., by surface plasmon resonance or biolayer interferometry) correlate with efficiency of viral entry and infectivity in vitro: higher affinity interactions typically lower the effective receptor density required for entry and expand the set of cell types the virus can infect. **[39]**. Glycosylation and affinity modulation: Viral glycosylation near receptor binding sites or host receptor glycosylation can sterically occlude or enhance affinity. For instance, glycan position on alphavirus E proteins influences MXRA8 engagement and thus alters infectivity of certain strains. **[40]**. Species-specific affinity differences: Minor sequence or structural differences in orthologous receptors across species (or even between breeds) can reduce or abrogate binding (e.g., bovine MXRA8 variants that fail to bind chikungunya), producing host-range barriers. **[41]**.

Tropism: cellular, tissue, and species consequences

Cell-type tropism arises from receptor distribution and co-factors. A virus with a strong affinity for a receptor will only infect tissues where that receptor is present at the right levels and where intracellular factors allow replication. This is why receptor expression maps (like MXRA8 in musculoskeletal tissues and AXL in some neural progenitors) can be used to predict tropism and disease symptoms. **[42]**. Receptor plasticity and emergence. Structural plasticity in viral receptor binding proteins (RBPs) can facilitate alterations in receptor utilization under selective pressure, allowing for expanded tropism or interspecies transmission a mechanism associated with host adaptation and emergence. **[43]**. Attachment factors influence initial dissemination. Lectins and heparan sulfate on skin or mucosal cells can trap incoming virions and make it easier for them to infect nearby cells or move to immune cells that can handle them (like DCs). This changes the way the virus spreads in the beginning. [44]

Experimental and structural approaches that reveal specificity/affinity

High-resolution structural biology: (cryo-EM, X-ray crystallography) of virion–receptor complexes has been critical to map interfaces and predict mutational effects on affinity and tropism. **[45]**. Functional assays: (neutralization by receptor-blocking antibodies, receptor knockout/knock-in cell lines, binding kinetics by SPR/BLI) together validate the structural predictions and quantify how alterations change tropism. **[46]**.

Implications for pathogenesis, surveillance, and therapeutics

Predicting emergence and host range**:** Mapping sequence variation in viral RBPs and host receptors across species helps predict which viruses may cross species barriers and which receptor changes confer expanded tropism. **[47]**. Therapeutic targeting: Blocking high-affinity receptor interactions (small molecules, receptor decoys, neutralizing antibodies) is a logical antiviral strategy; however, redundancy of attachment factors and receptor plasticity pose challenges. **[48]**. Understanding molecular specificity and affinity of arbovirus–receptor interactions is central to explaining tropism at cell, tissue, and species levels, guiding both surveillance for emergent strains and design of receptor-targeted interventions. Structural and biophysical tools combined with functional virology remain the most powerful way to link single-residue changes to epidemiologically relevant shifts in tropism.

Therapeutic and experimental implications of structural receptor data

Rational inhibitor design: High-resolution receptor–virus complexes (e.g., MXRA8–CHIKV) reveal atomic contact networks suitable for small molecules, receptor-blockading antibodies, or receptor decoys. PDB entries and cryo-EM maps enable in silico docking and epitope mapping for neutralizing antibodies. **[4]**. Host-directed vs virus-directed strategies: Targeting host attachment factors (e.g., blocking DC-SIGN, TIM/TAM, HSPG interactions) may reduce the chance of viral escape but raises safety concerns because those receptors have physiological roles (e.g., apoptotic cell clearance). Conversely, virus-directed antibodies that occlude receptor-binding sites (epitope blocking) can be highly specific. **[49]**. Arboviruses (for example, dengue virus [DENV], Zika virus [ZIKV], West Nile virus, chikungunya virus) enter host cells by binding attachment factors and bona-fide entry receptors on susceptible cells; notable receptor families include C-type lectins (e.g., DC-SIGN), phosphatidylserine (PS) binding proteins such as TIM (TIM-1, TIM-4) and TAM receptors (AXL, Tyro3), heat-shock proteins and other cell-surface molecules. Blocking receptor–virus interactions is a validated antiviral strategy for multiple arboviruses. **[50]**.

Therapeutic approaches that target receptors or receptor usage

Blocking antibodies and receptor antagonists

Monoclonal antibodies (mAbs) can neutralize virus by binding viral envelope proteins or by blocking host receptors required for entry. Human and murine mAbs that block viral envelope epitopes have shown cross-neutralizing activity between dengue and Zika in preclinical work, reducing infection and disease in animal models. Antagonistic antibodies directed against host receptors (e.g., anti-AXL) or small-molecule inhibitors may reduce viral entry in vitro. However, host-directed blockade must balance antiviral benefit against physiological roles of the receptor (e.g., AXL in tissue homeostasis). **[50]**.

Soluble receptor decoys and engineered binding traps

Soluble receptor ectodomains or engineered decoy proteins can sequester virus particles preventing interaction with cell-surface receptors. Soluble forms of PS-binding domains or engineered Fc-fusion receptor fragments have been proposed as entry-blocking therapeutics for PS-mediated “apoptotic mimicry” used by flaviviruses. Decoy approaches aim to reduce viral tropism without permanently altering host cells. (50)

Oligonucleotide therapies (siRNA, antisense, ribozymes) to downregulate receptor expression

Antisense oligonucleotides and small interfering RNAs (siRNAs) targeting host receptor mRNAs (for example, AXL or TIM family transcripts) can reduce receptor expression and thereby lower susceptibility to infection in cell models. Oligonucleotide therapies face delivery and off-target challenges but provide a modular, sequence-specific way to transiently lower receptor levels in target tissues. (51)

CRISPR-based and gene-editing approaches

CRISPR–Cas technologies can be used ex vivo to knock out critical host factors in permissive cell lines (or engineered tissue grafts) to produce virus-resistant cells. In vivo gene editing to remove a widely expressed receptor carries substantial safety and ethical concerns and

is not yet clinically feasible, but it remains a powerful research tool to validate receptors as therapeutic targets. **[51]**.

Aptamers, nanobodies and small binding scaffolds

Aptamers (nucleic-acid ligands) and single-domain antibodies (nanobodies) can be selected to bind viral envelope proteins or host receptors with high affinity, blocking entry. Aptamers have advanced in stability and delivery, and nanobodies offer small size, tissue penetration, and ease of engineering for intranasal or localized delivery. Both modalities are under active preclinical development for flaviviruses and alphaviruses. **[55]**.

Small-molecule inhibitors and host pathway modulators

Small molecules that alter receptor trafficking (e.g., modifying ubiquitination or endocytosis of TIM receptors) or inhibit receptor tyrosine kinase activity (for TAM receptors) can reduce virus entry and post-entry steps. Repurposed kinase inhibitors have been tested in cell-culture screens; however, specificity and host toxicity are major limiting factors. **[52]**.

Evidence and examples

TIM-1 and dengue: TIM-1 is involved in the endocytosis of the dengue virus. Changing TIM-1 through genetics or drugs makes it harder for the virus to get into cells, which supports TIM-1 as a potential treatment target. AXL and Zika: AXL was found to be a major way that ZIKV gets into different types of cells, such as skin and neural progenitors. Blocking AXL with antibodies or knocking it down with siRNA lowers ZIKV infection in vitro, but the importance of this in vivo depends on the tissue and model. Alphavirus receptors: Recent discoveries of new protein receptors for alphaviruses and the tick-borne encephalitis virus have opened up more options for therapeutic targets and shown that there are many different types of receptors in arbovirus families. **[53]**.

Problems with translation

Trade-offs between host functions— Blocking all of the body's receptors at once could be bad because many of them are important for normal body functions (for example, TAM receptors help control the immune system). The best choice is targeted delivery or temporary modulation. **[8]**. Virus redundancy and plasticity—Arboviruses often employ various attachment factors and

receptors; obstructing a single receptor may be inadequate if alternative entry pathways are available. Combination strategies, such as direct antivirals and receptor blockade, may be necessary. Delivery and stability: Oligonucleotides, aptamers, and biologics need delivery systems that work well (like nanoparticles and conjugates) to get to the right tissues (like the skin, placenta, and CNS) safely. **[51]**. ADE and immune modulation—For flaviviruses, immune phenomena such as antibody-dependent enhancement make it harder to design therapeutic antibodies. Receptor-targeted therapies should not accidentally make infection worse or mess up immunity. (50) A suggested plan for development

Target validation: use CRISPR screens and genetic knockdown in human cells and organoids that are physiologically relevant to find receptors that have a big effect on viral entry and a low risk of harming the host. **[53]**. Choosing a modality: for receptors that work outside of cells, choose soluble decoys, nanobodies, or monoclonal antibodies; for receptors that work inside cells, think about oligonucleotides or small molecules that change how things move around. Localized delivery: look into topical or intranasal delivery (to the skin or mucosa) for places where arthropods have bitten and optimized carriers for delivering to the placenta or CNS when appropriate (like ZIKV). **[58]**. Preclinical safety: check how blocking receptors affects immune homeostasis and tissue repair in animal models before moving on to humans. Targeting arbovirus entry through host receptors is a promising strategy that works well with direct-acting antivirals and vaccines. A successful therapeutic program should focus on carefully validating targets, choosing the right modality based on receptor biology, and delivery strategies that reduce toxicity to the host while blocking important entry points. Ongoing improvements in aptamers, nanobodies, oligonucleotides, and receptor structural biology are making more options available for translational development. **[57]**.

Conclusions:

Arboviruses causing hemorrhagic fever exploit diverse cellular host receptors for entry, including transferrin receptor 1 (TfR1) for New World clade B arenaviruses like Machupo and Junin viruses, DC-SIGN and nucleolin for Crimean-Congo Hemorrhagic Fever Virus (CCHFV), and multiple factors such as FcγRs, C-type lectins, integrins (e.g., αvβ3), laminin receptors, and glycosaminoglycans like heparan sulfate for flaviviruses including dengue (DENV), West Nile (WNV), and yellow fever virus (YFV). These receptors help with attachment, clathrin-mediated

endocytosis, and pH-dependent fusion. Because they are redundant, they can work with a wide range of immune cells, endothelial cells, and epithelial tissues. This helps the virus spread, avoid the immune system, and cause bleeding.

Structural studies show how MXRA8's Ig-like domains fit into alphavirus E1-E2 spikes (like chikungunya virus) and how phosphatidylserine receptors (TIM/TAM families) let flaviviruses mimic apoptosis, changing innate immunity and making it easier for them to enter cells by using low-pH endosomal triggers. Receptor expression patterns dictate cell-type tropism—e.g., MXRA8 in musculoskeletal tissues for alphaviruses, DC-SIGN on dendritic cells for flaviviruses—explaining disease manifestations like hemorrhage, arthritis, and encephalitis, with mutations or adaptations promoting zoonotic spillover. Heparan sulfate proteoglycans and other attachment factors gather virions and then switch to high-affinity receptors to bring them inside.

Targeting these receptors holds antiviral potential: soluble decoys (e.g., MXRA8-Fc), blocking antibodies, siRNAs, aptamers, and small-molecule inhibitors disrupt entry interfaces elucidated by cryo-EM structures, diminishing infection in models with minimal localized toxicity. Receptor redundancy, physiological roles (e.g., TAM in homeostasis), antibody-dependent enhancement (ADE) in flaviviruses, and viral plasticity are all problems that need to be solved with combination therapies, CRISPR-validated targets, and tissue-specific delivery. Genome-wide screenings and proteomics persist in discovering new receptors, such as LDLRAD3, for Venezuelan equine encephalitis virus (VEEV). Progress in structural biology, haploid screens, and organoid models will elucidate receptor hierarchies, maturation effects, and host polymorphisms that affect emergence. Combining these ideas helps with surveillance, receptor decoys, and broad-spectrum interventions that strike a balance between safety and effectiveness.

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